

Figure 1

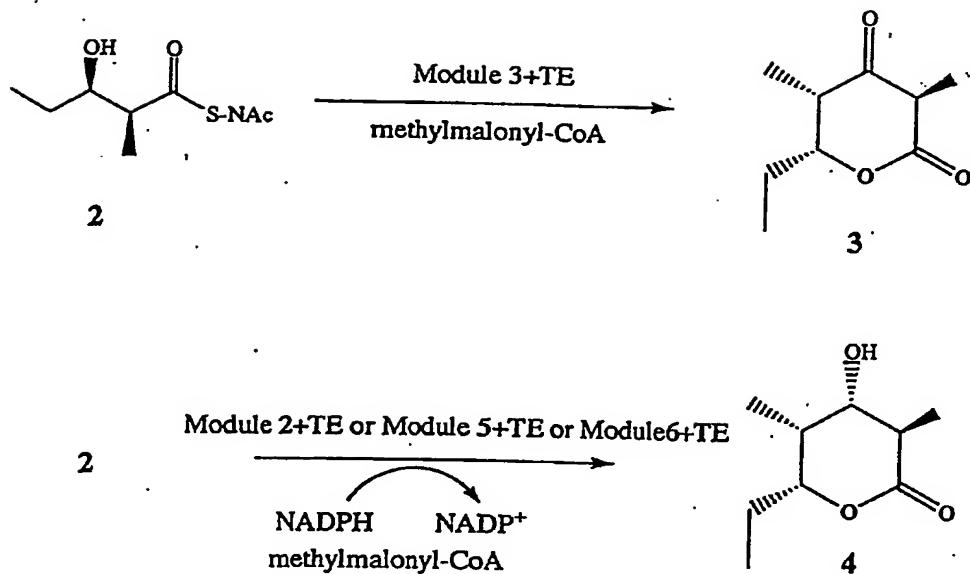


Figure 2

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**(a) INTRA-POLYPEPTIDE LINKER**

M2ery: GGATGAEQAAPATT..APVD  
M4ery: VGDAD..QAA.VRVVGAA.DES  
M6ery: VGAAEAEQA.PALVREVPKDAD  
M2rif: FGSA.A.NR.PAEIGTAAAE  
M3rif: LG..ER.PAAPAPVTRDVSD  
M5rif: GETVAGAPATPVTTVADAG  
M3rap: .ELFTGENPAPVRGPVSAVGQD  
M4rap: .ELFTGENPAPVRGPVSVVGQD  
M7rap: .ELFTGENPAPVRGPVSA.GQD

**(b) N-TERMINAL INTER-POLYPETIDE LINKER**

M3ery: .....VTD SE KVAEYLRR .ATLDLRAAR QRIRE..LES  
M5ery: MSGDNGM.TE E.KLRRYLKR TVT.ELDSVT ARLRE..VEH RAG  
M4rif: .....MSAPNE QIVDAL.R ASLKE....N VRLOQENSAL AAAAA  
M7rif: .....VSASYE KVVEAL.R KSLEE....V GTLKKNRQL ADAAG  
M8rif: .....V.AD EGQLRDYLKR .AIADARDAR TRLRE..VEE QAR  
M9rif: .....MATD E.KLLKYLKR .VTAELHS... .LRKQGARH .AD  
M5rap: .....MR.. EDQLLDAL.R KSVKE....N ARLRKANTSL RAAMD  
M11rap: .....M.PEQD KVVEYL.R WATAELHTTR AKL....EA LAAANT

Figure 3

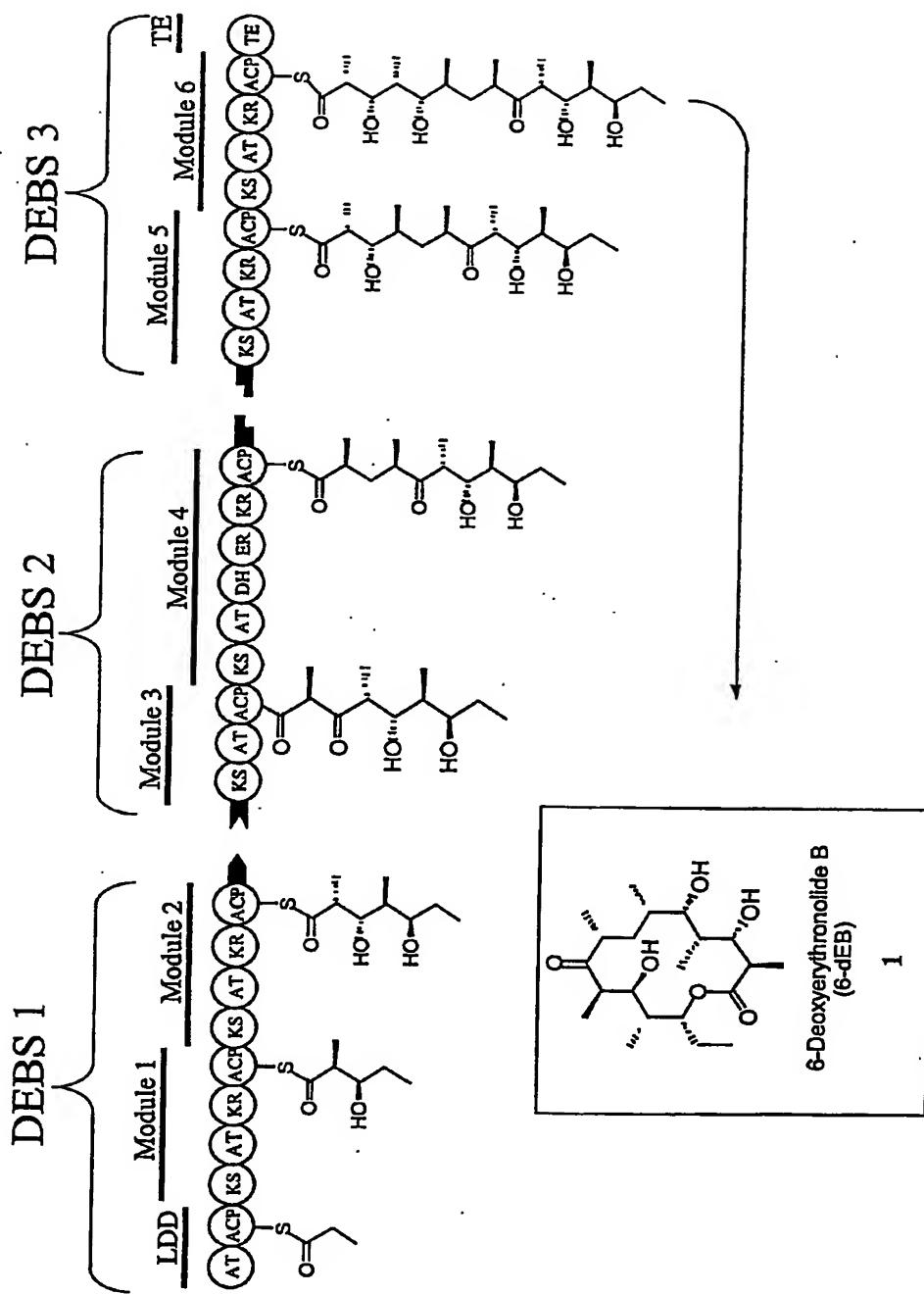


Figure 4

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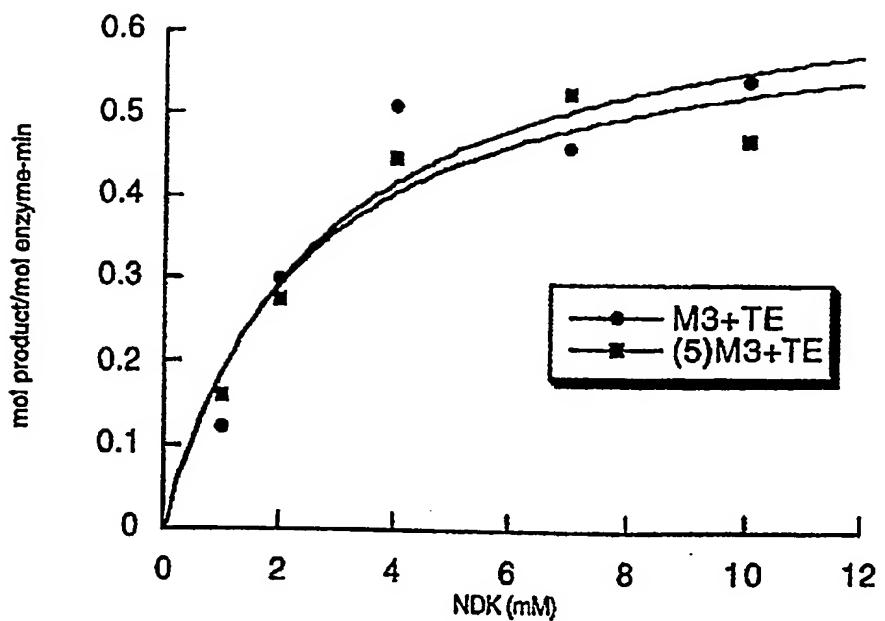
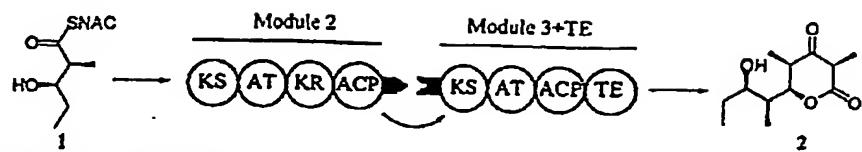
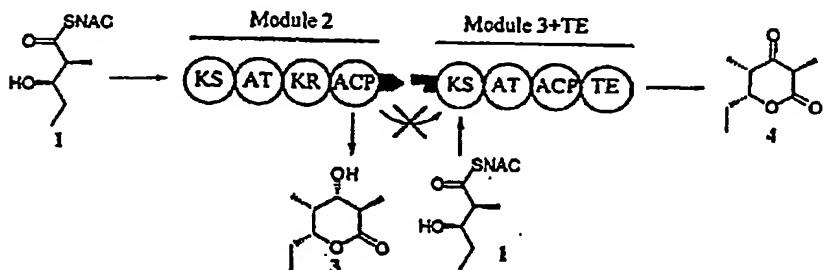


Figure 5

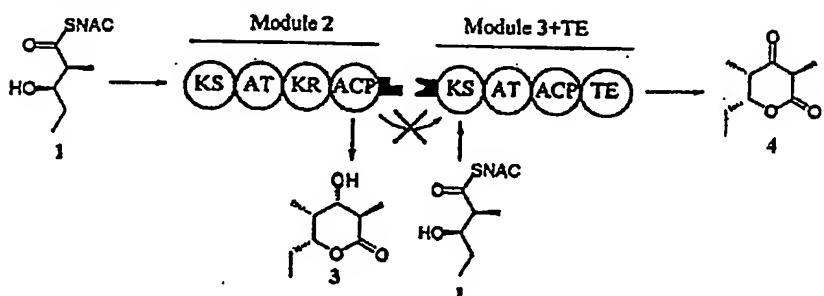
**A. M2 and M3+TE**



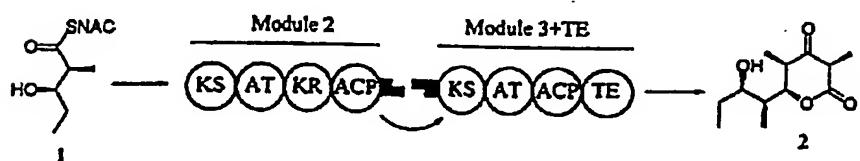
**B. M2 and (5)M3+TE**



**C. M2(4) and M3+TE**



**D. M2(4) and (5)M3+TE**



**Figure 6**

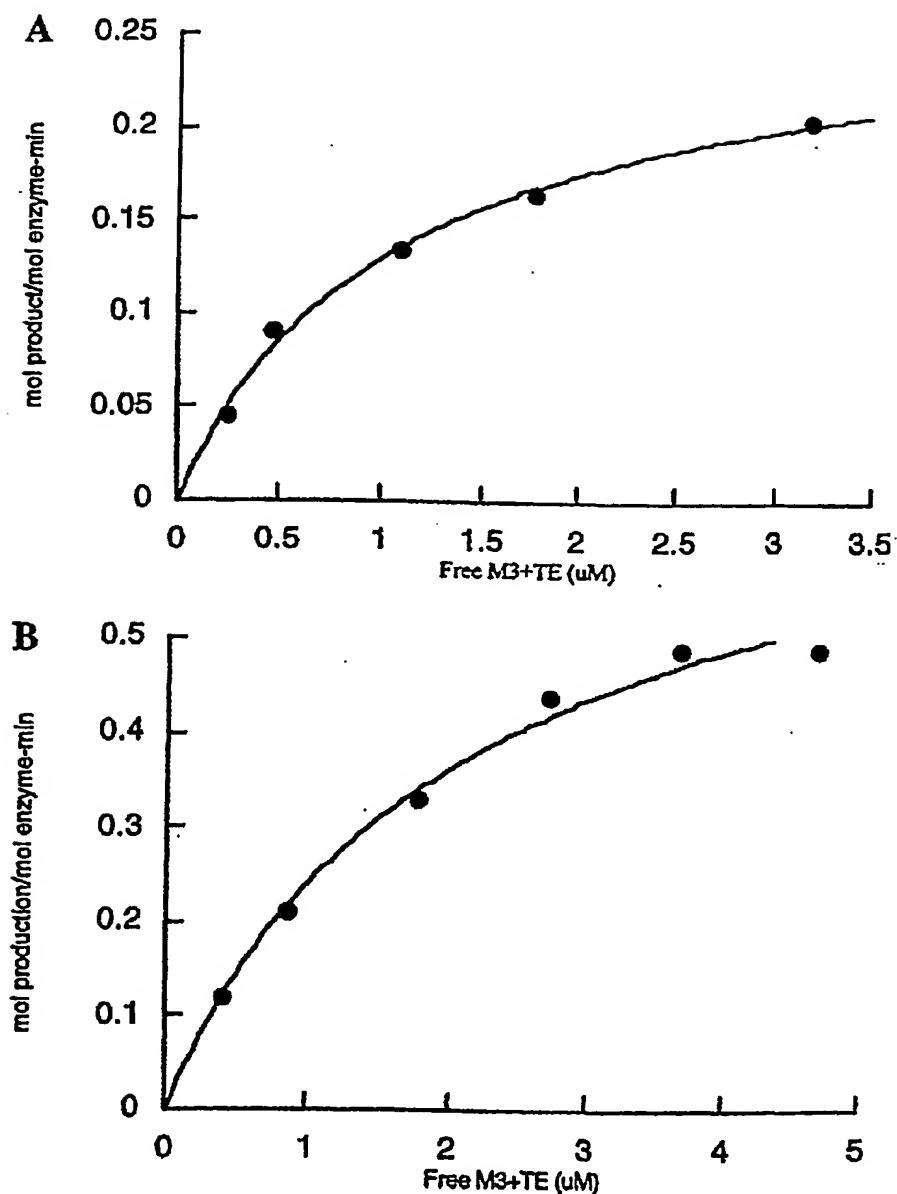


Figure 7

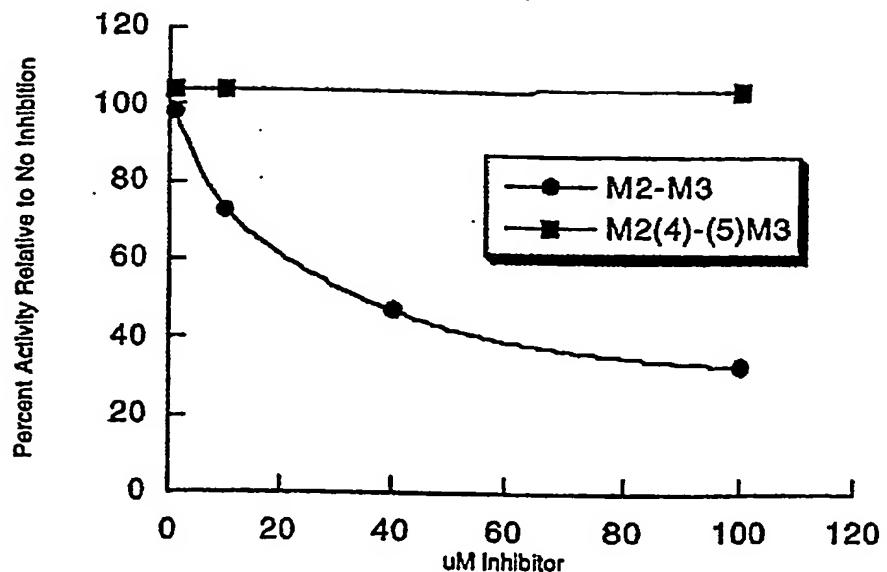


Figure 8

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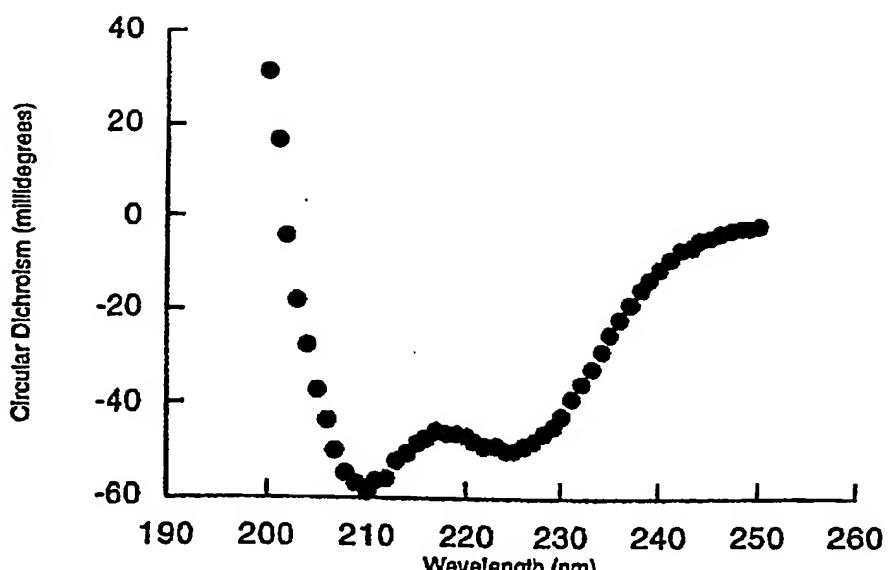
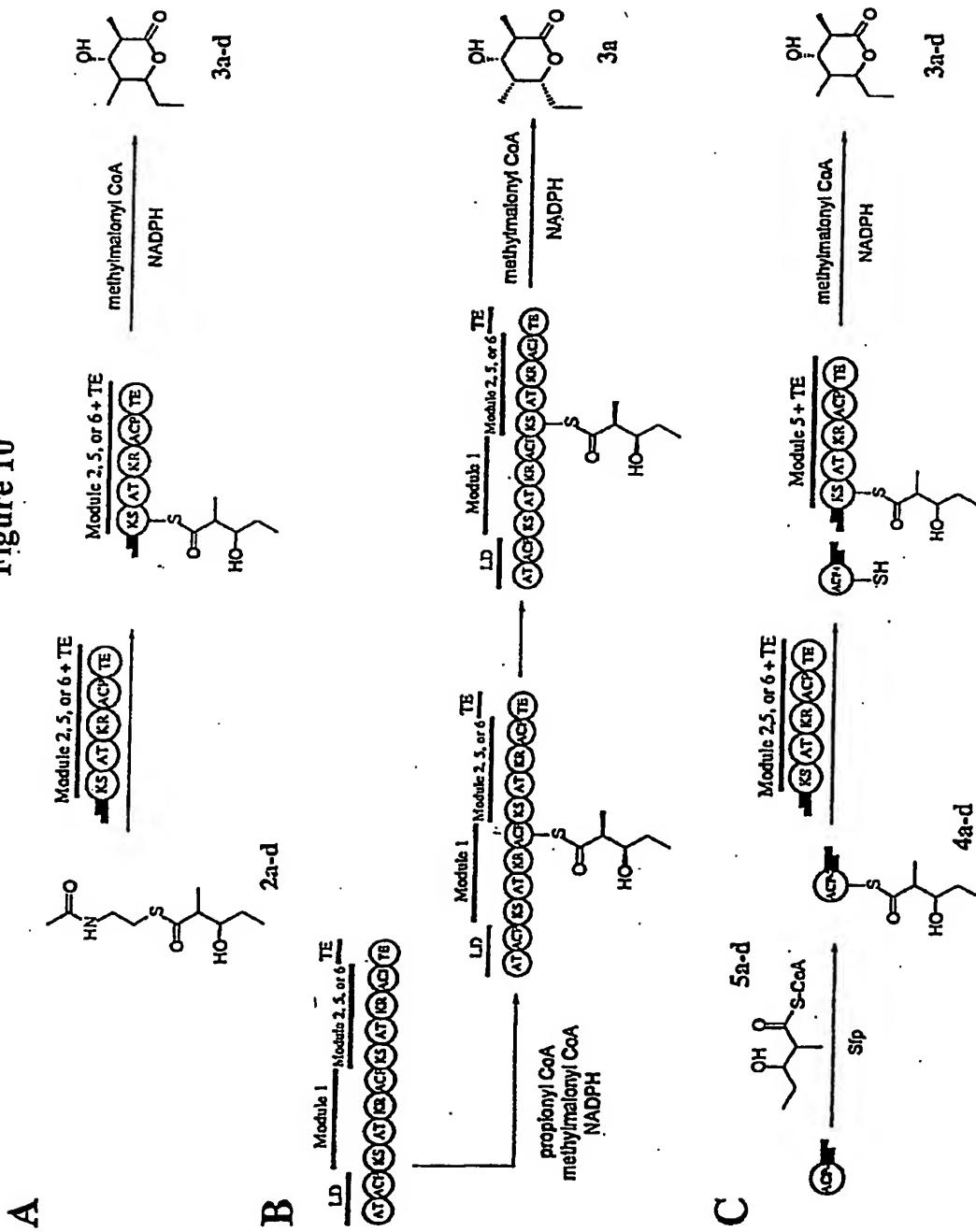
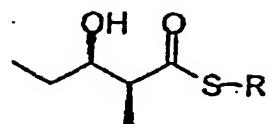


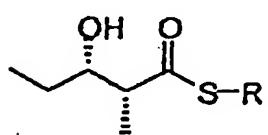
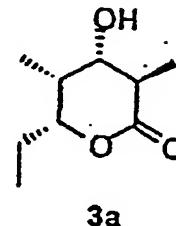
Figure 9

Figure 10



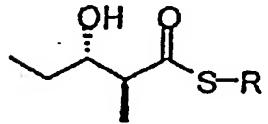
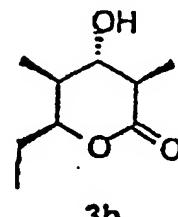


2a: R=N-acetylcysteamine  
4a: R=Acy1 carrier protein



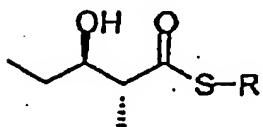
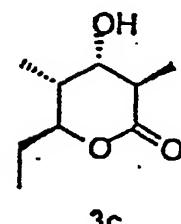
2b: R=N-acetylcysteamine  
4b: R=Acy1 carrier protein

Module 2+TE  
or  
Module 5+TE  
or  
Module 6+TE



2c: R=N-acetylcysteamine  
4c: R=Acy1 carrier protein

methylmalonyl CoA  
NADPH



2d: R=N-acetylcysteamine  
4d: R=Acy1 carrier protein

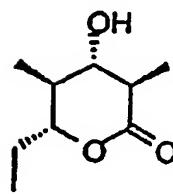


Figure 11

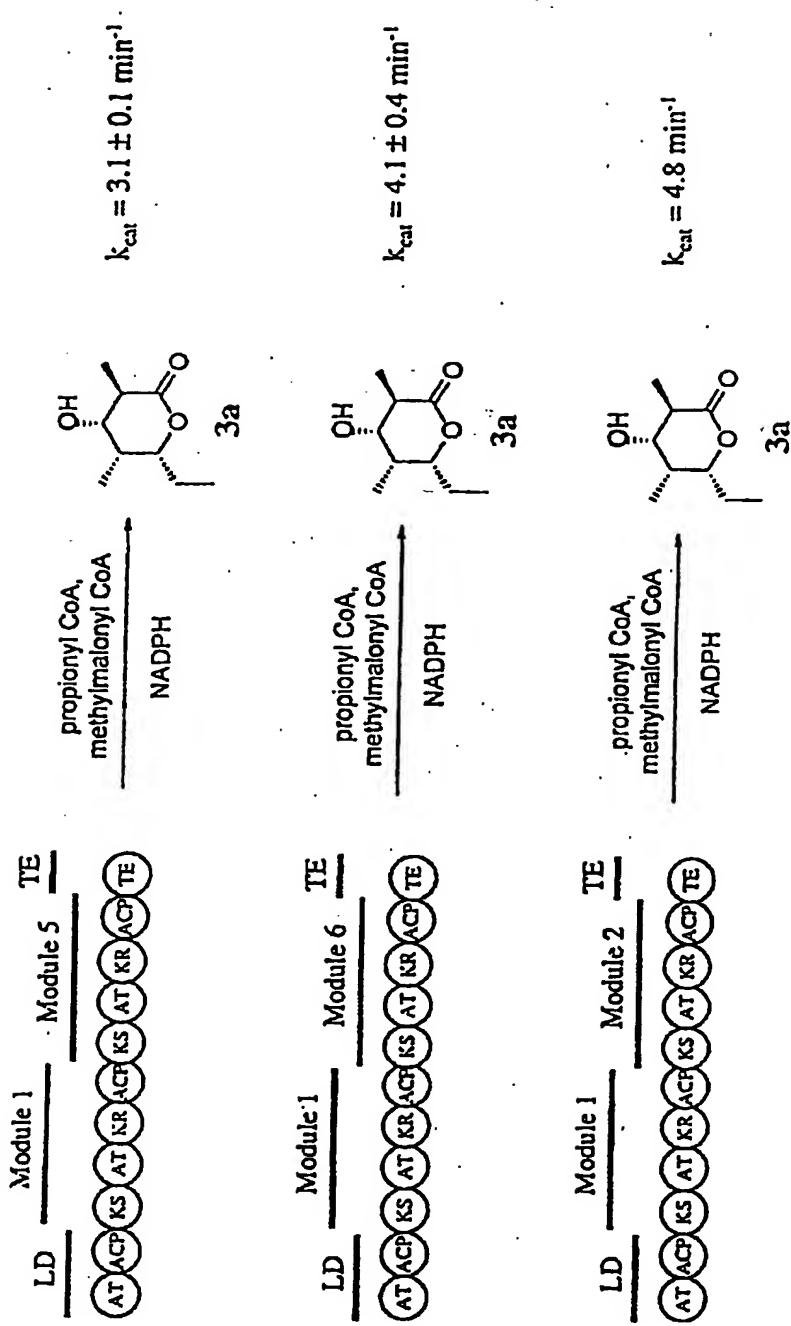


Figure 12

| Substrate | (5)Module 2 + TE<br>KS AT KR ACP TE | (5)Module 5 + TE<br>KS AT KR ACP TE | (5)Module 6 + TE<br>KS AT KR ACP TE |               |
|-----------|-------------------------------------|-------------------------------------|-------------------------------------|---------------|
| 4a        |                                     | 2900 ± 500                          | 290 ± 50                            | 340 ± 60      |
| 4b        |                                     | 18 ± 1                              | 3.9 ± 0.7                           | 85 ± 15       |
| 2a        |                                     | 0.75 ± 0.01                         | 0.016 ± 0.002                       | 1.1 ± 0.1     |
| 2b        |                                     | 0.0076 ± 0.0006                     | 0.0011 ± 0.0001                     | 0.058 ± 0.006 |

Figure 13

| Substrate | (S)Module 2 + TE |                 | (S)Module 5 + TE |                 | (S)Module 6 + TE |                 |
|-----------|------------------|-----------------|------------------|-----------------|------------------|-----------------|
|           | KS AT KR ACP TE  | KS AT KR ACP TE | KS AT KR ACP TE  | KS AT KR ACP TE | KS AT KR ACP TE  | KS AT KR ACP TE |
| 4a        |                  | 6.7 ± 0.2       | > 9.3 ± 1.4      | > 10 ± 1        |                  |                 |
| 4b        |                  | > 0.97 ± 0.02   | > 0.48 ± 0.02    | > 3.4 ± 0.4     |                  |                 |
| 4c        |                  | > 1.0 ± 0.1     | > 1.4 ± 0.1      | > 2.1 ± 0.2     |                  |                 |
| 4d        |                  | > 0.29 ± 0.03   | > 0.20 ± 0.01    | > 1.9 ± 0.1     |                  |                 |
| 2a        |                  | > 4.6 ± 0.6     | 0.24 ± 0.01      | 17 ± 2.9        |                  |                 |
| 2b        |                  | 0.25 ± 0.02     | 0.017 ± 0.001    | 2.4 ± 0.2       |                  |                 |
| 2c        |                  | N. D.           | N. D.            | N. D.           |                  |                 |
| 2d        |                  | N. D.           | N. D.            | N. D.           |                  |                 |

Figure 14

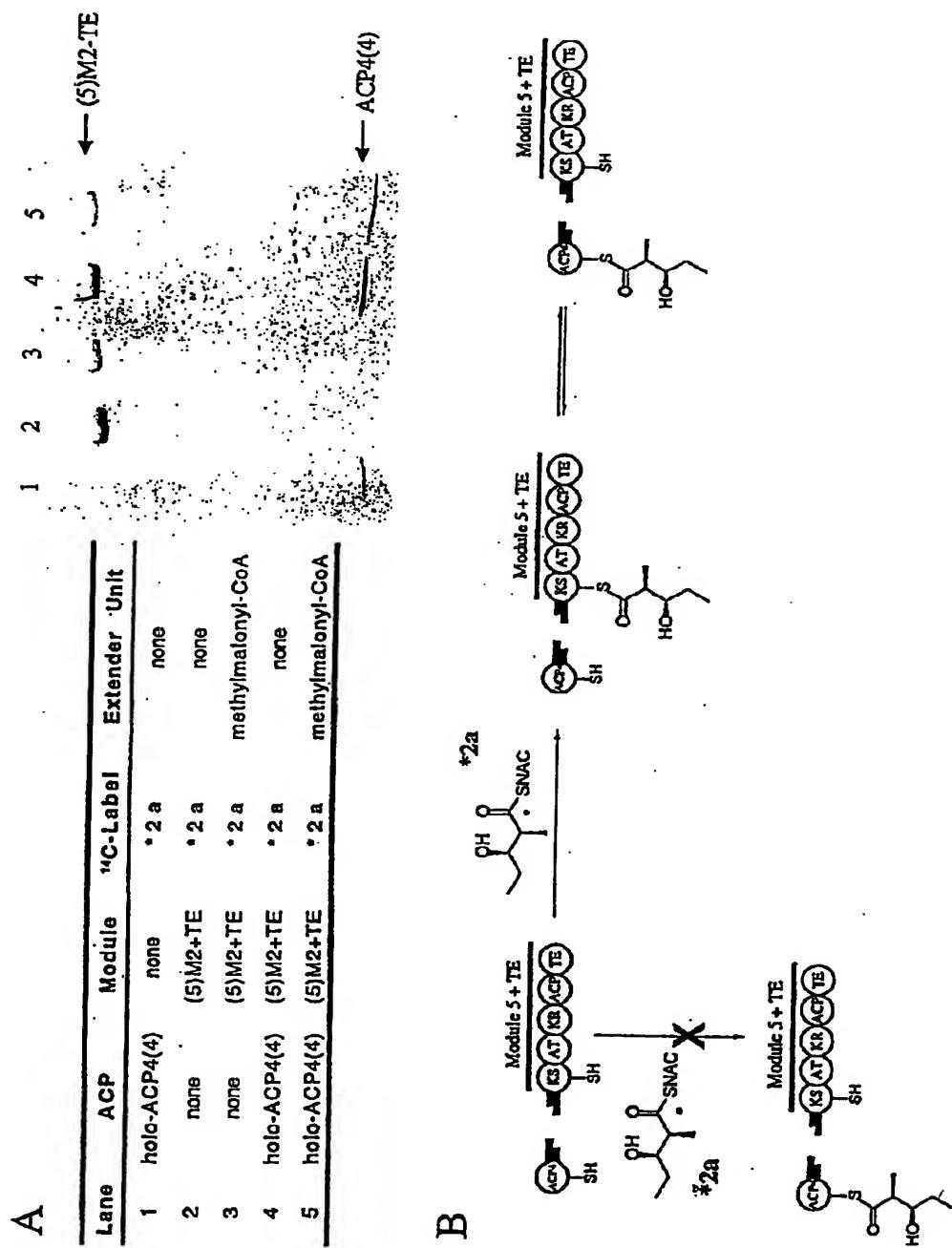


Figure 15

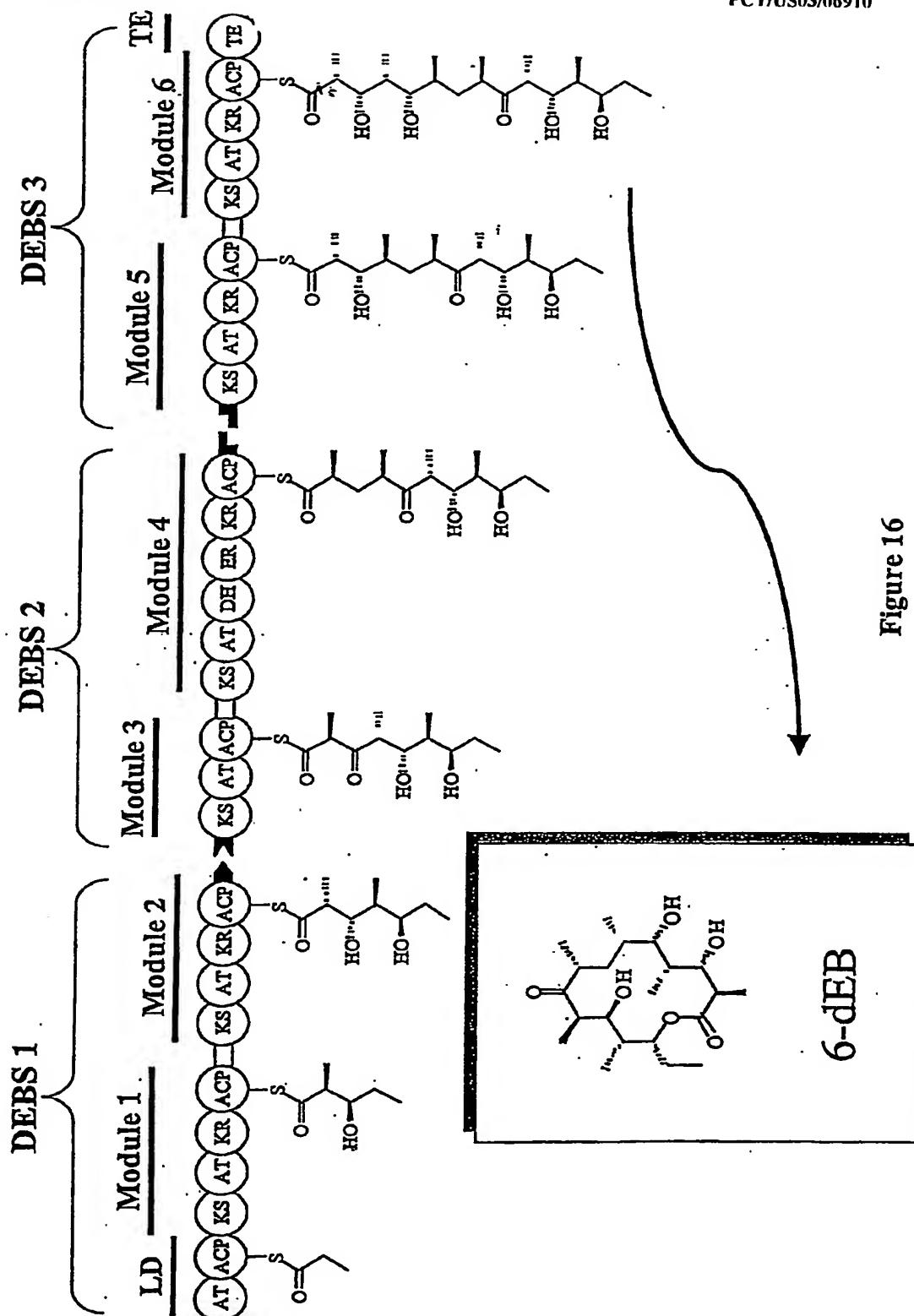


Figure 16

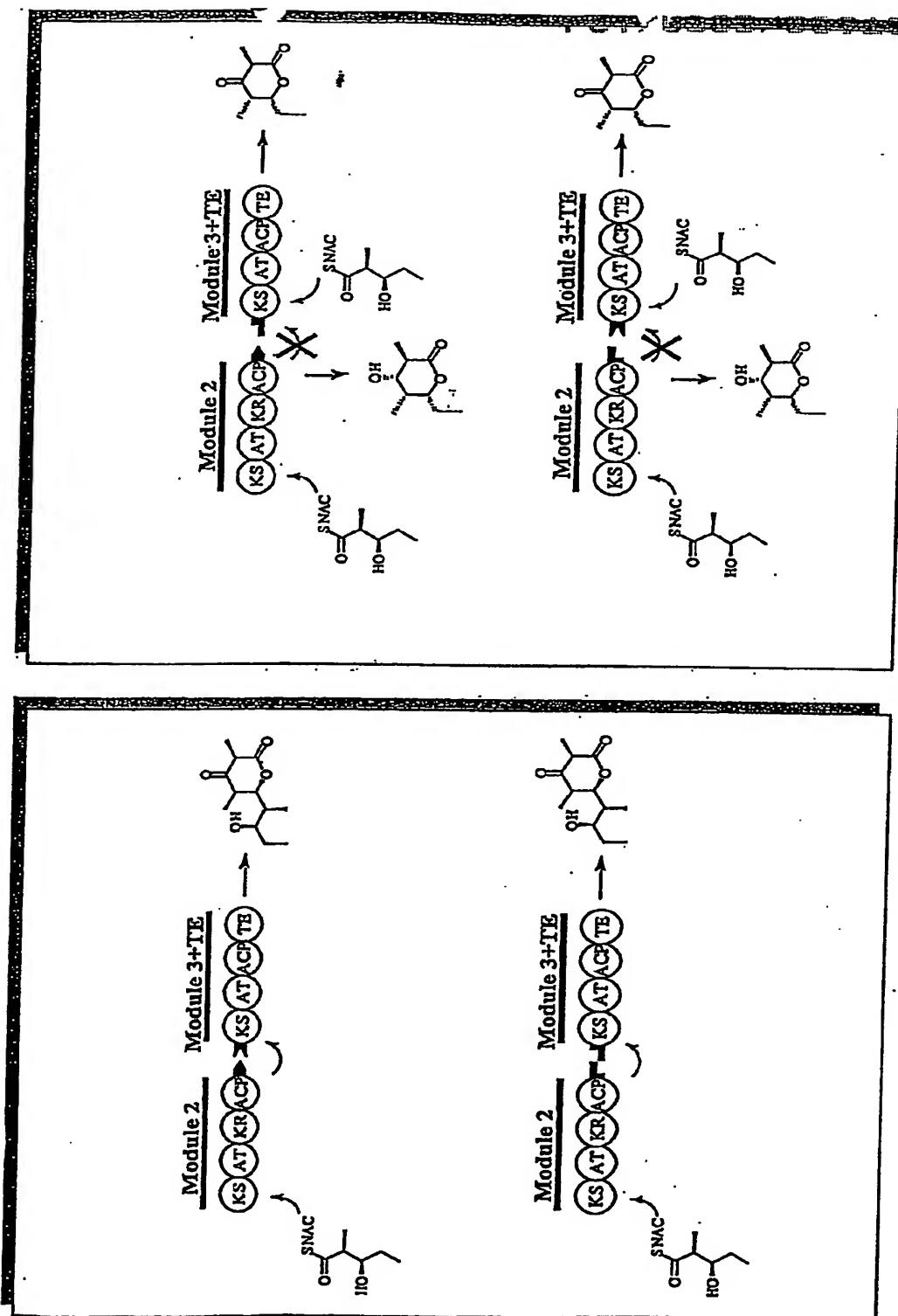


Figure 17

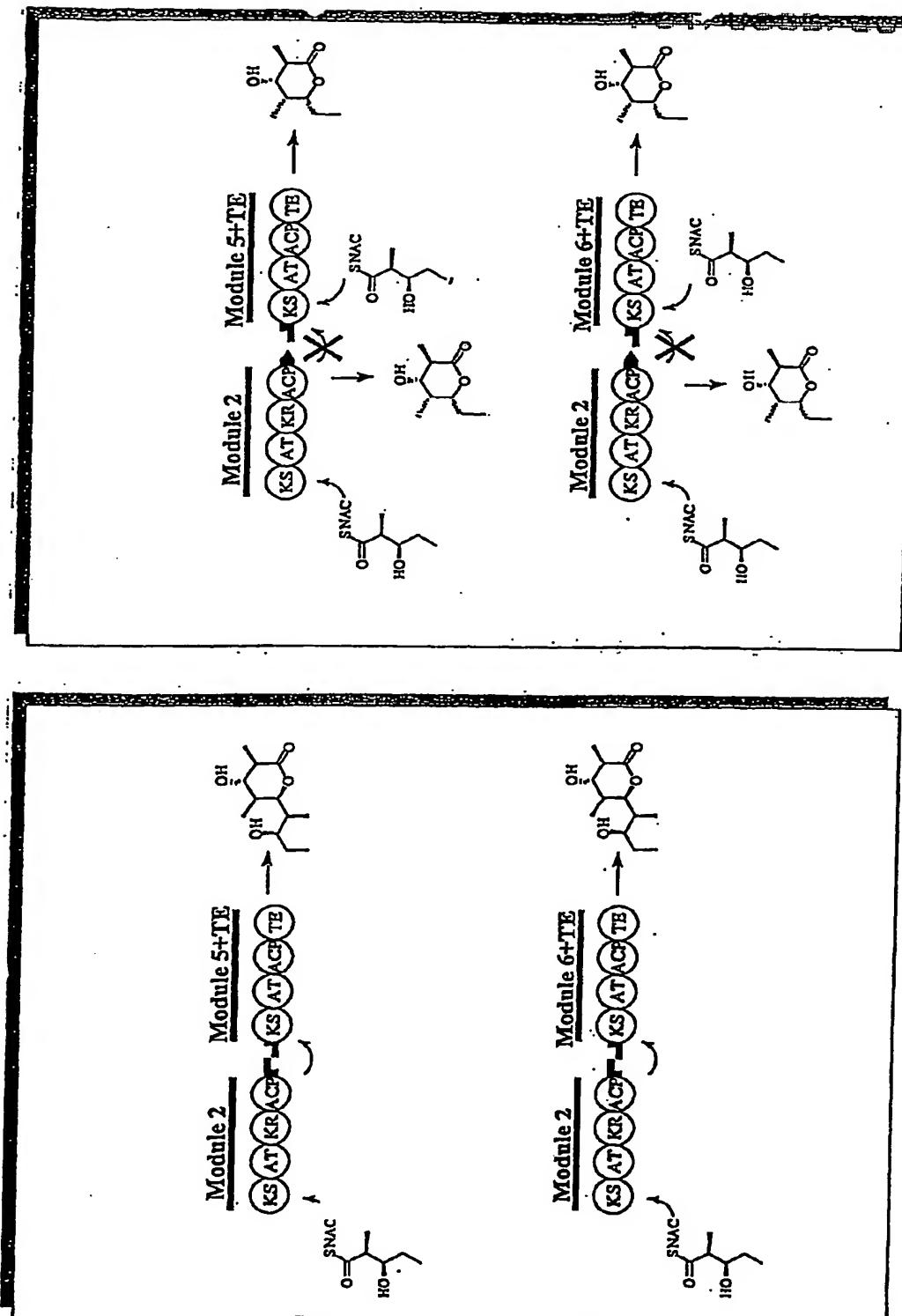


Figure 18

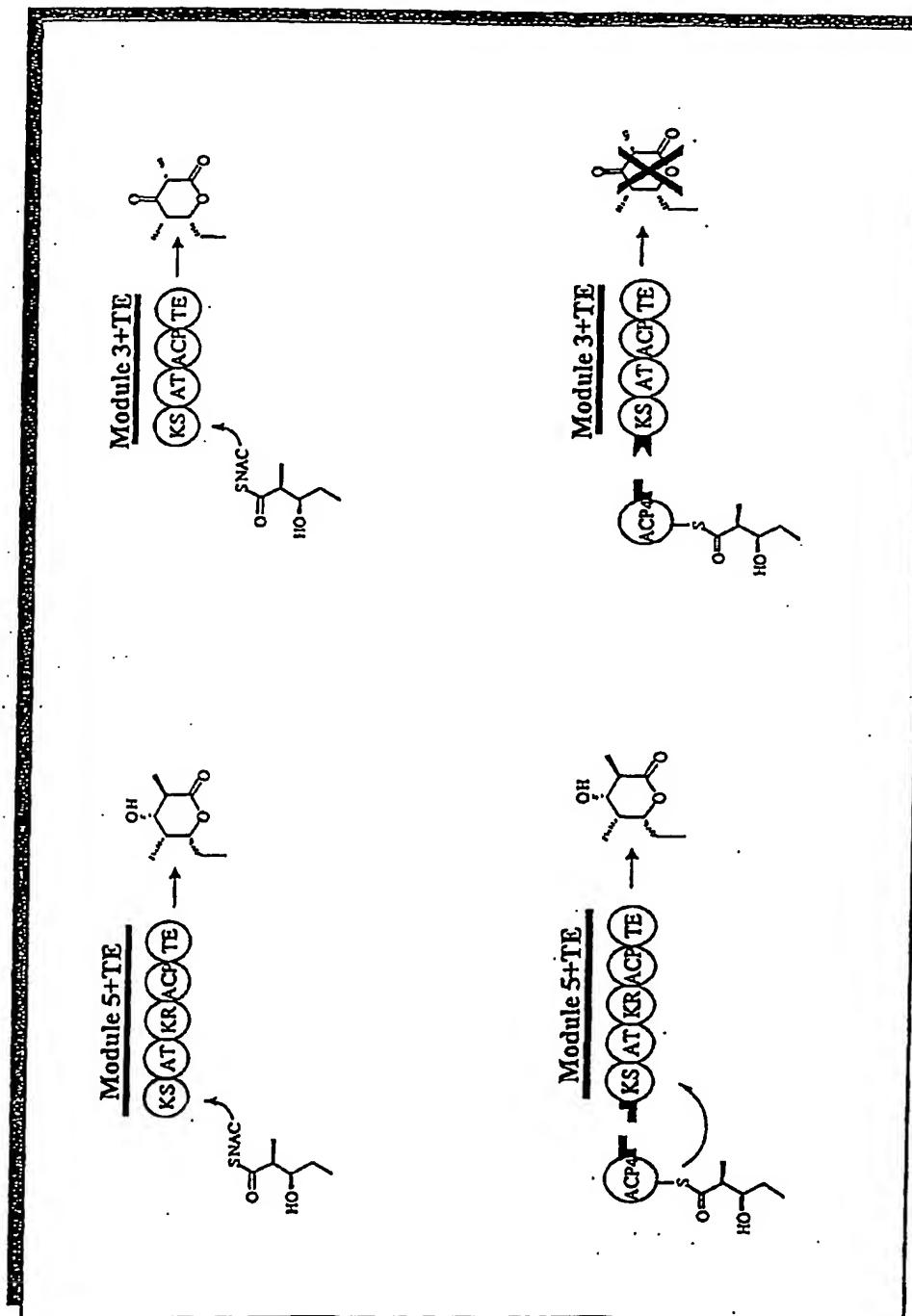


Figure 19

Figure 20

| Enzyme \ Substrates          |  |  |  |  |  |  |  |
|------------------------------|--|--|--|--|--|--|--|
| Module 2 + TE<br>(KSATKDKTE) |  |  |  |  |  |  |  |
| Module 5 + TE<br>(KSATKDKTE) |  |  |  |  |  |  |  |

Figure 21

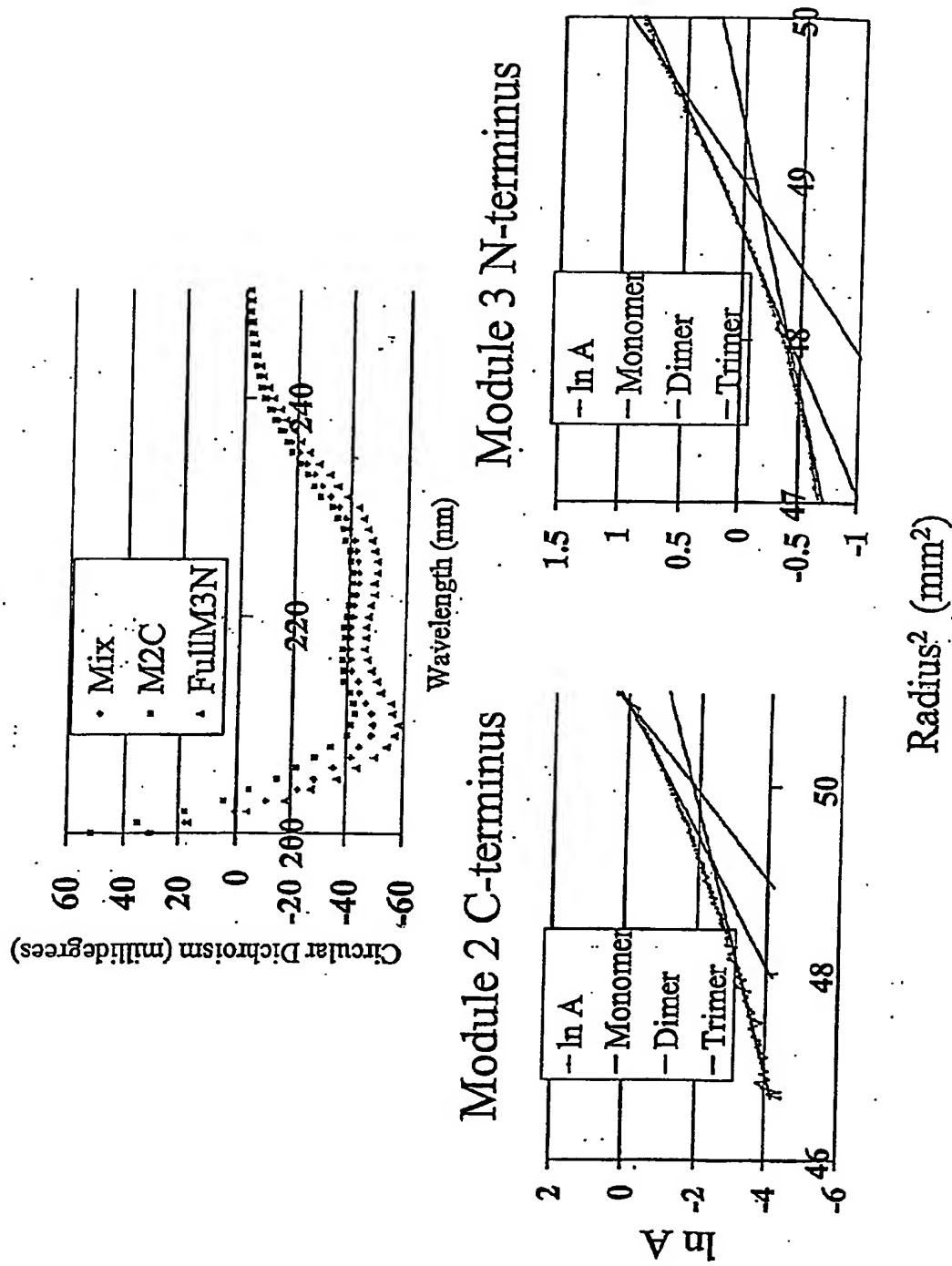
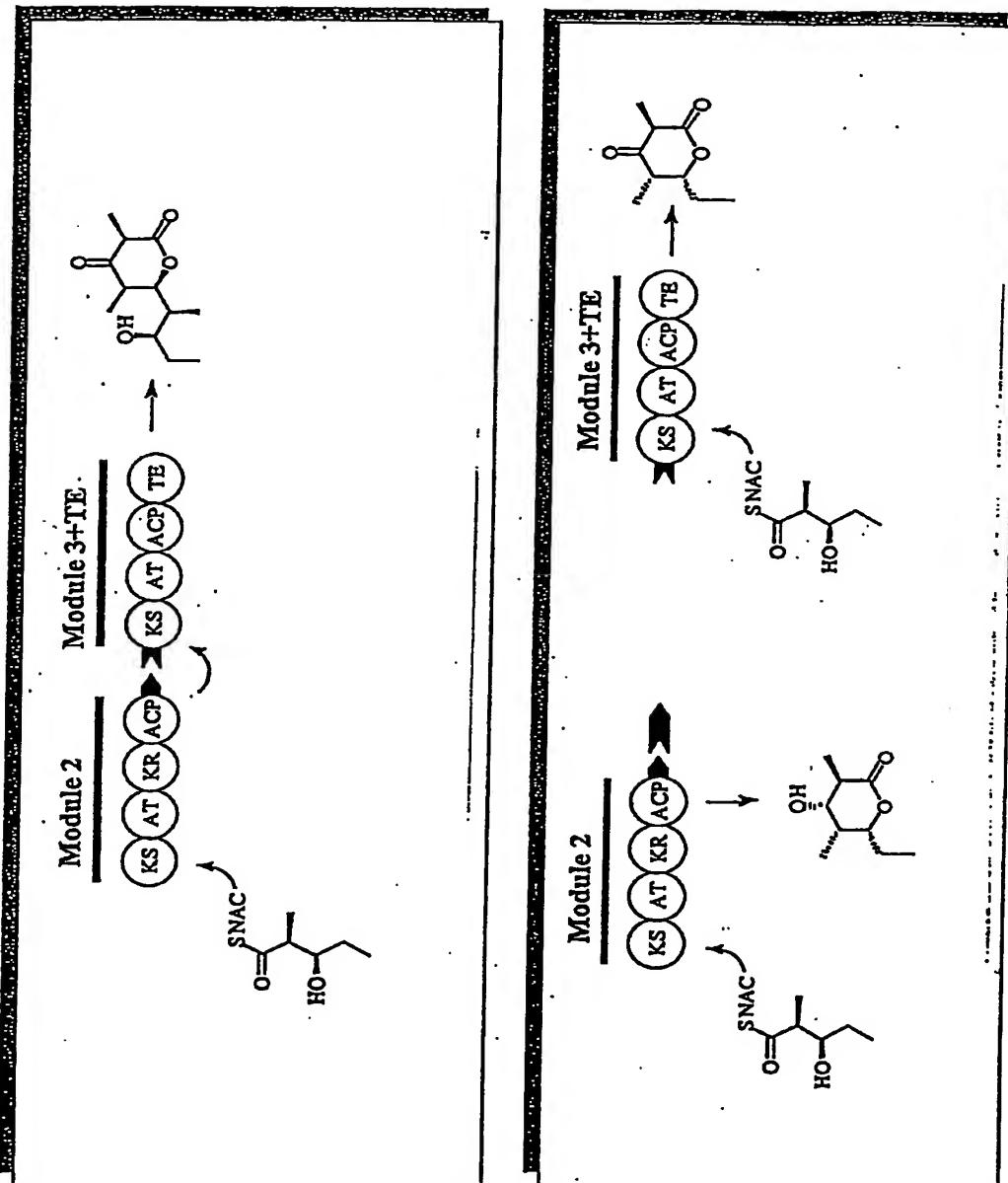


Figure 22



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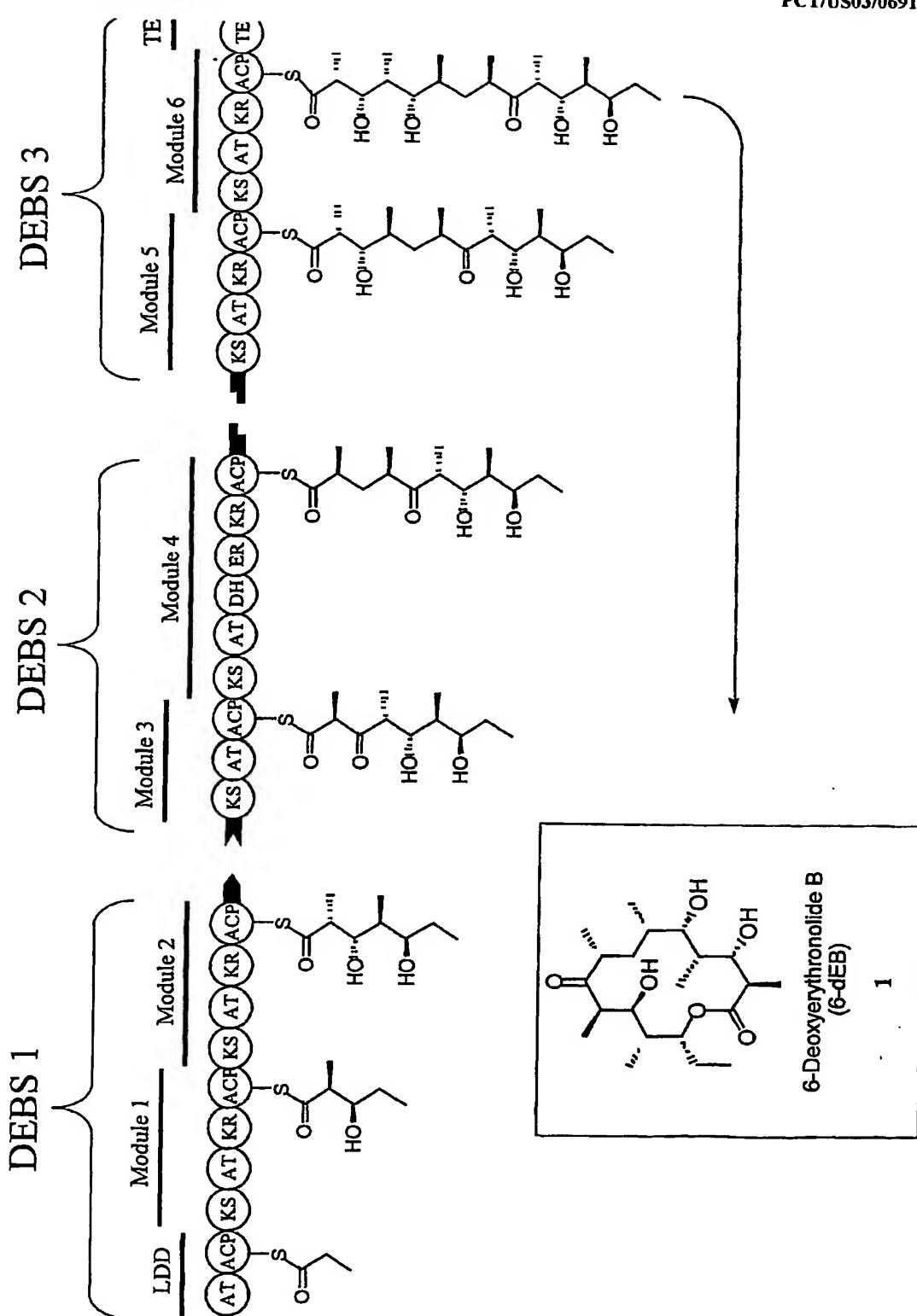


Figure 23

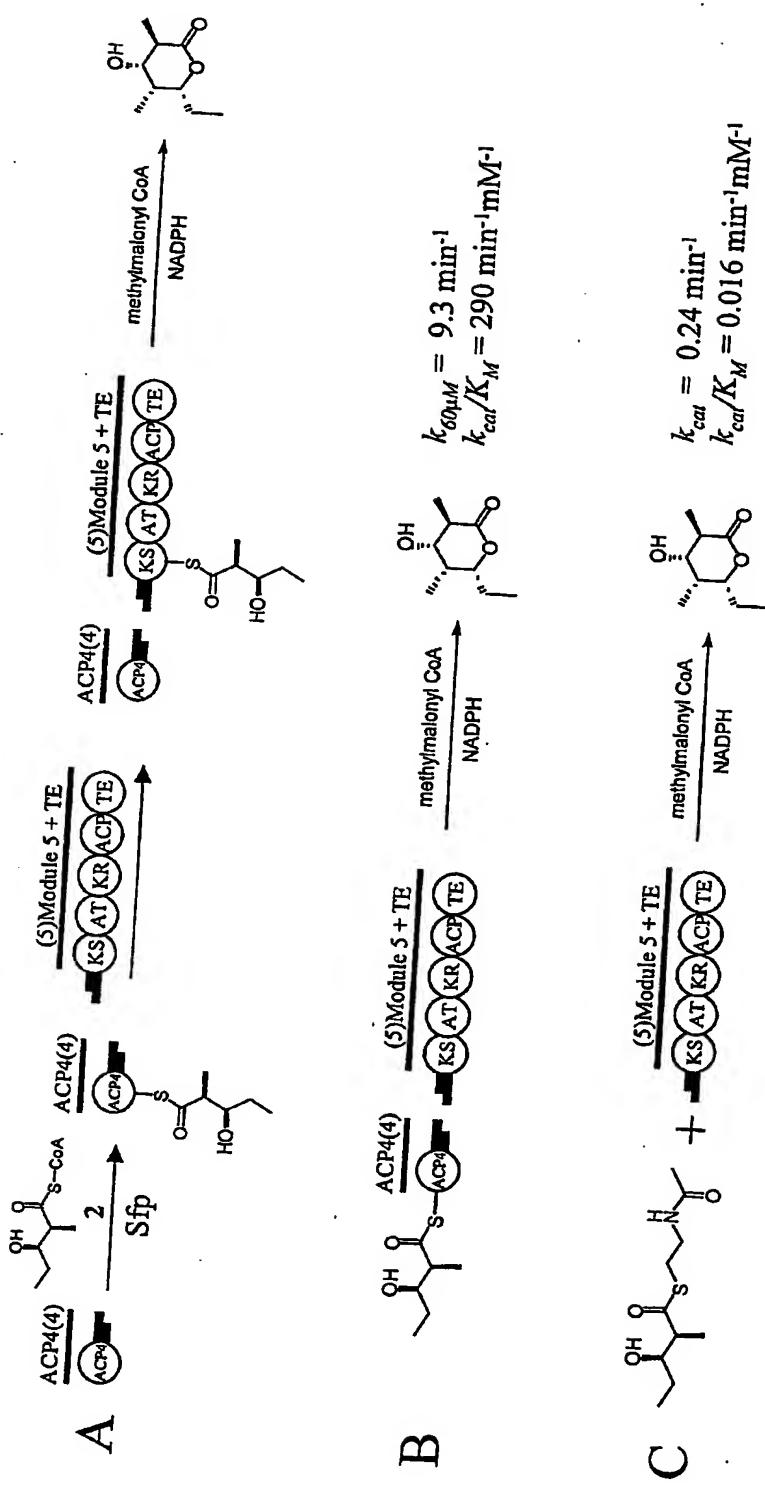


Figure 24

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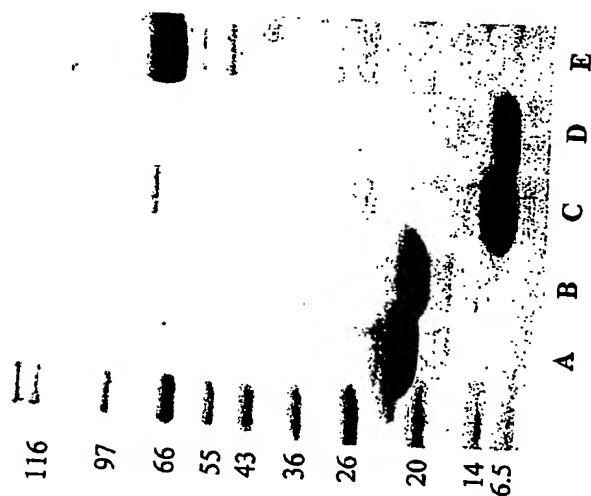


Figure 25

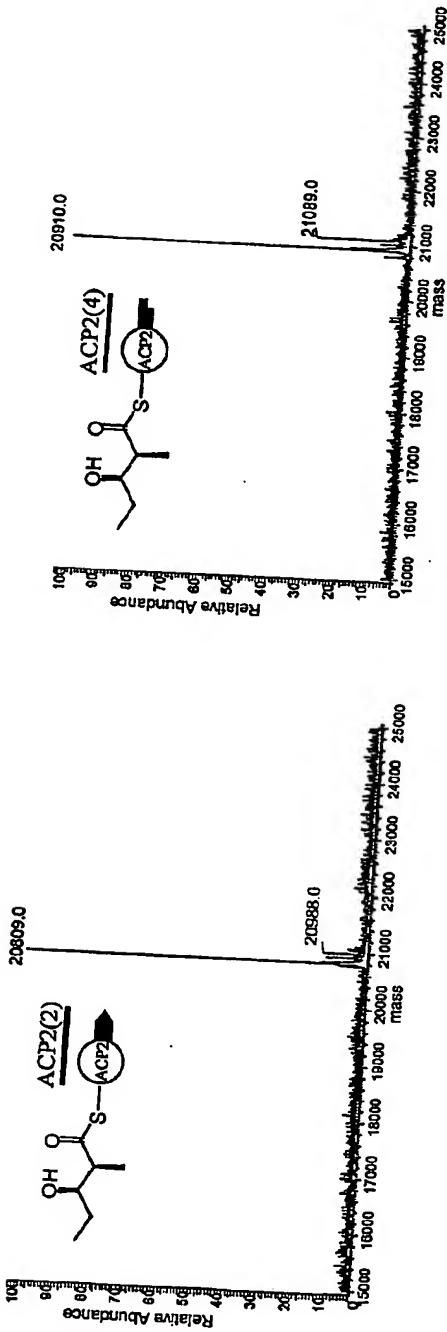
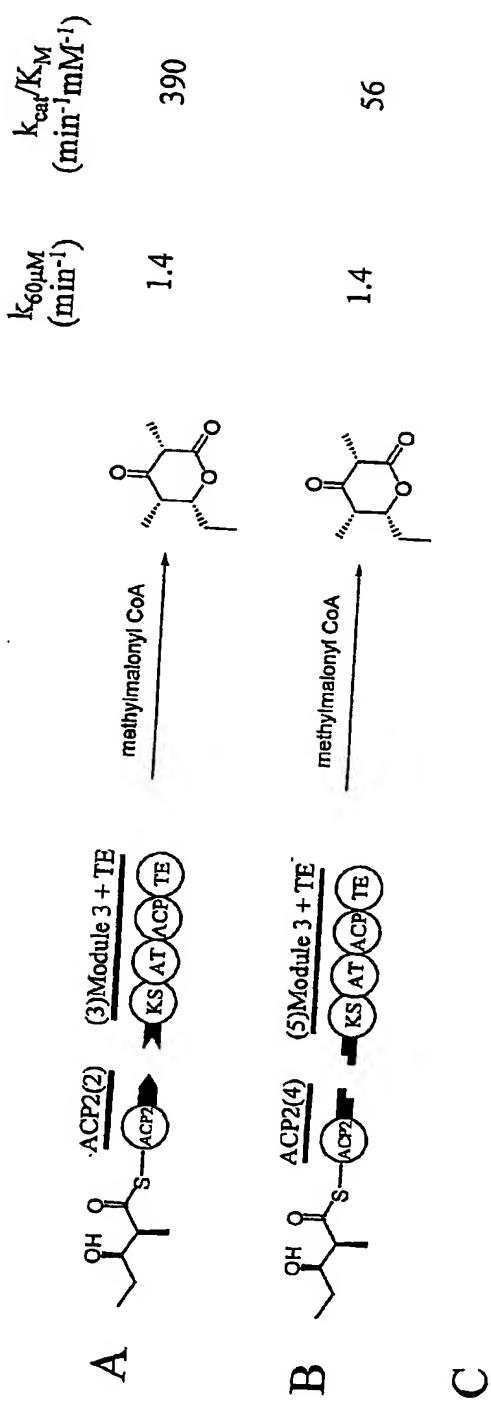


Figure 26

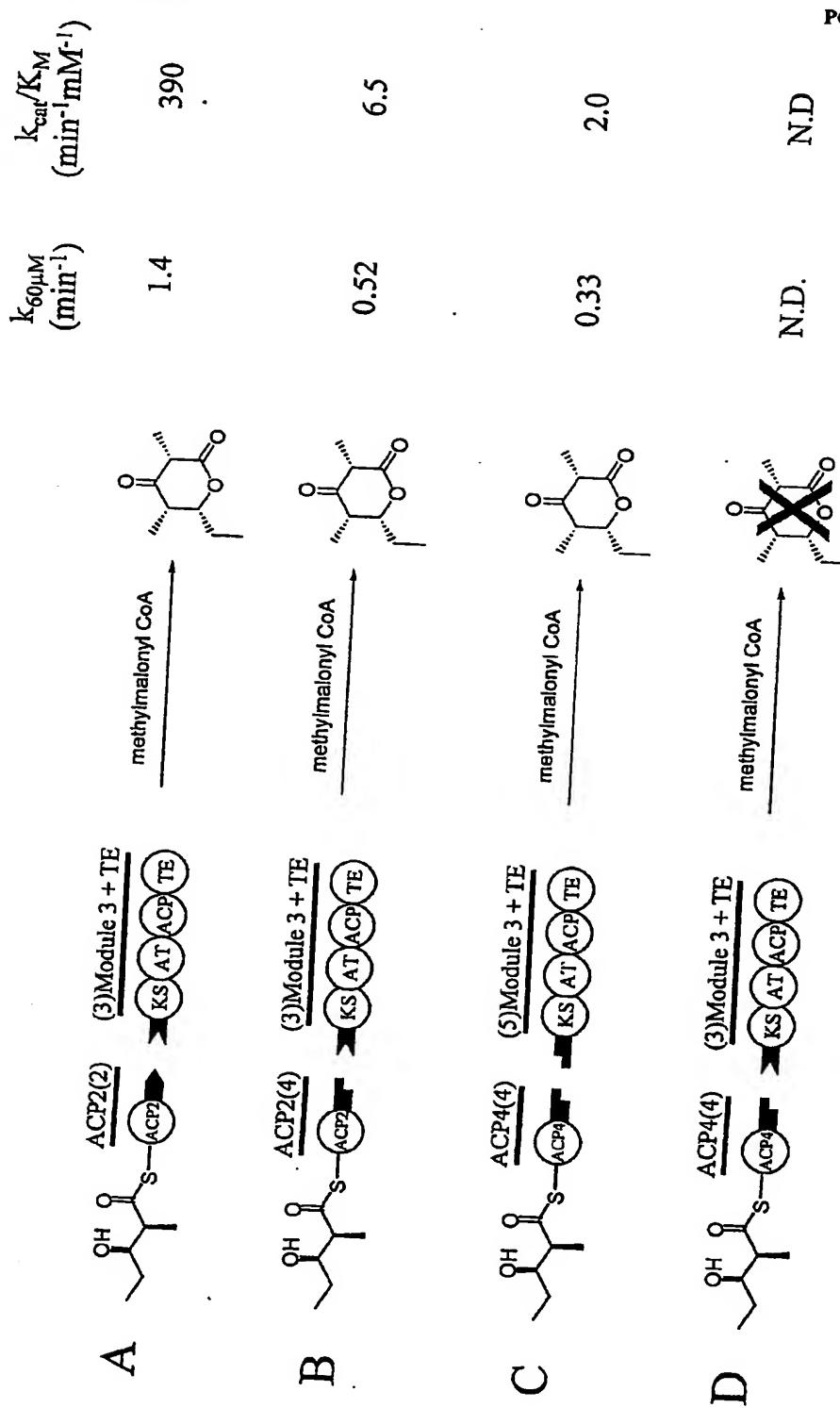


Figure 27

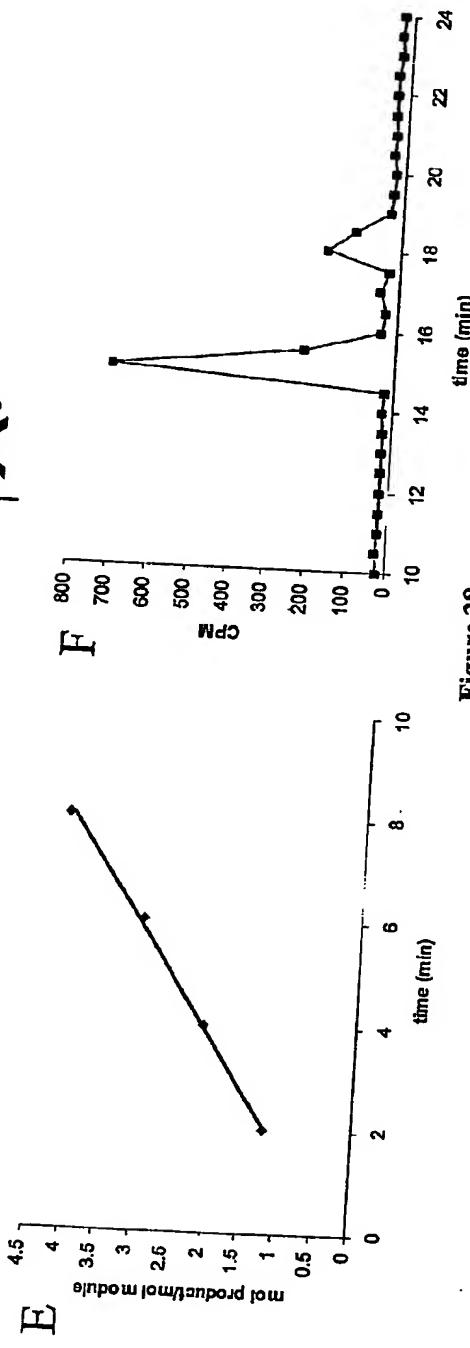
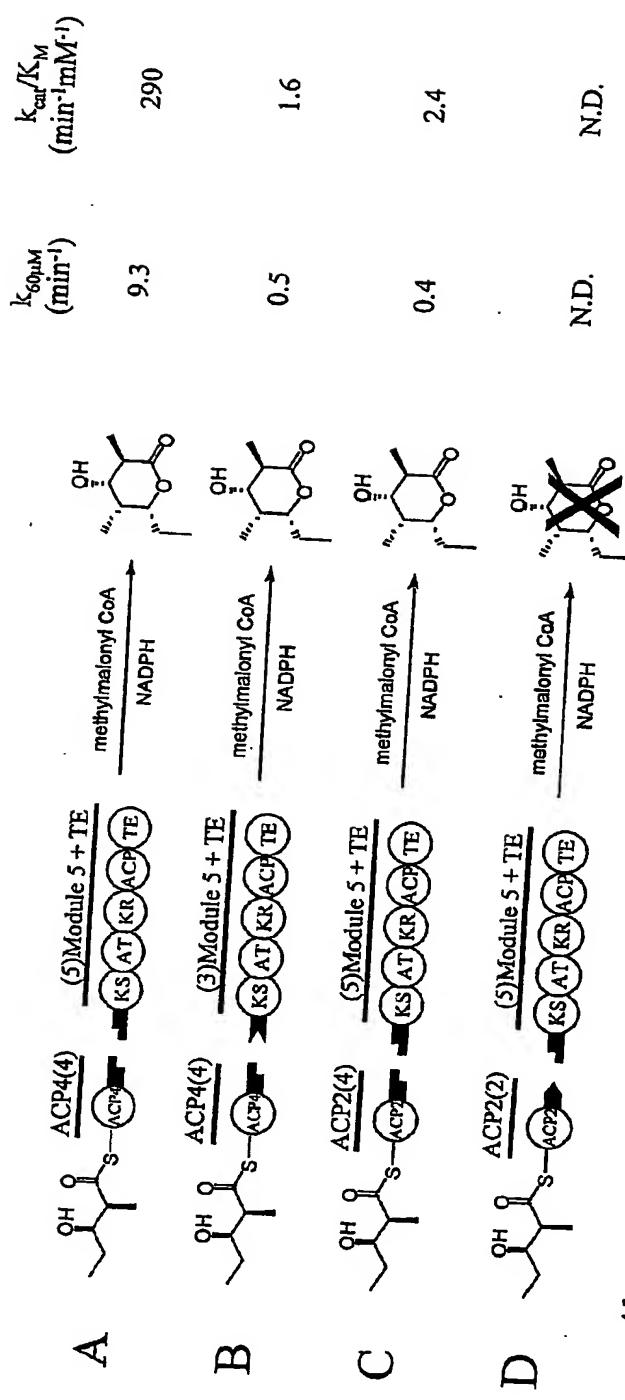


Figure 28

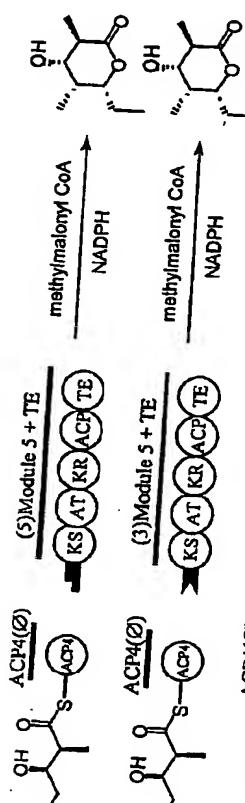
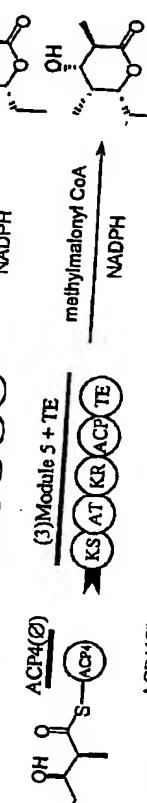
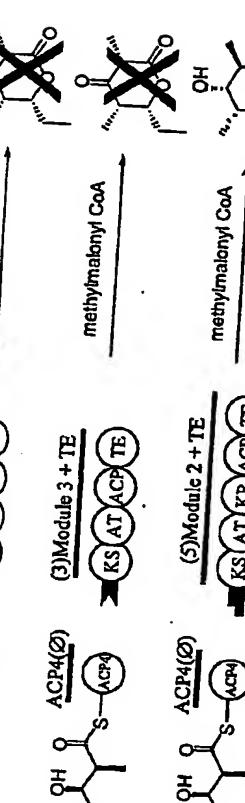
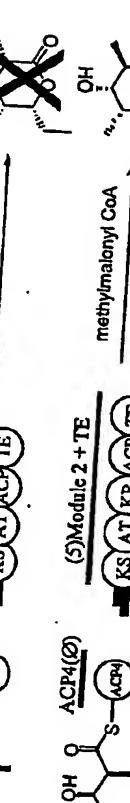
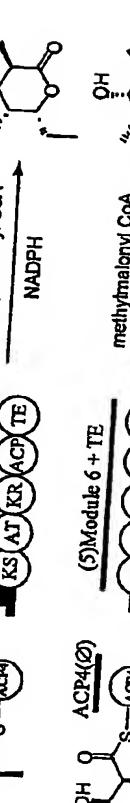
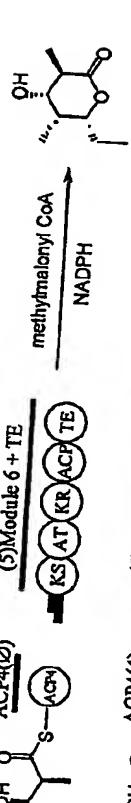
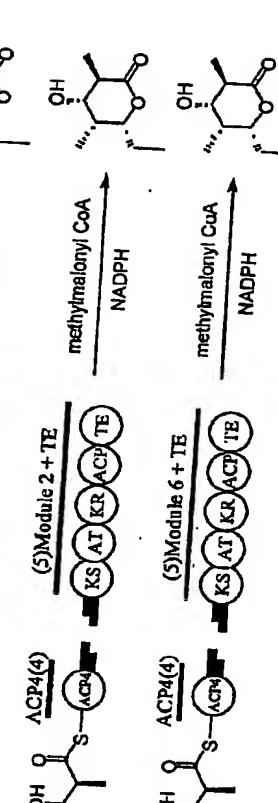
|   |                                                                                     | $k_{cat}/K_m$<br>(min <sup>-1</sup> mM <sup>-1</sup> ) | (min <sup>-1</sup> mM <sup>-1</sup> ) |
|---|-------------------------------------------------------------------------------------|--------------------------------------------------------|---------------------------------------|
| A |   | 0.49                                                   | 4.1                                   |
| B |   | 0.27                                                   | 2.5                                   |
| C |   | N.D.                                                   | N.D.                                  |
| D |   | N.D.                                                   | N.D.                                  |
| E |   | 0.44                                                   | 11                                    |
| F |   | 0.44                                                   | 11                                    |
| G |   | 0.11                                                   | 5.2                                   |
| H |  | 6.7                                                    | 2900                                  |
|   |                                                                                     | 10                                                     | 340                                   |

Figure 29

|          |                  |  |   |   |
|----------|------------------|--|---|---|
| <b>A</b> | <u>NovH(4)</u>   |  | ✓ | ✓ |
|          | <u>NovH(2)</u>   |  | ✗ | ✗ |
|          | <u>erylDD(2)</u> |  | ✓ | ✓ |
|          | <u>ACP2(2)</u>   |  | ✓ | ✓ |

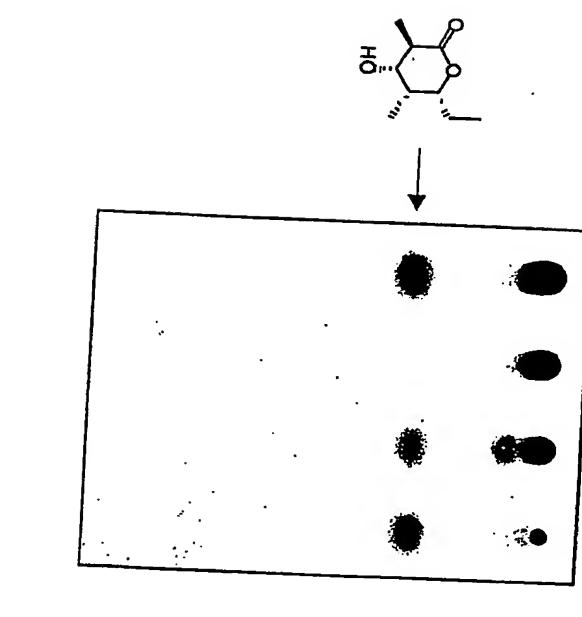


Figure 30

Figure 31 A

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|   |                                                                                                                            |                                     |       |
|---|----------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-------|
| 1 | .....ALESA GARVRELWUD ARGGDELAB BIRSV.GR.V AGVLSLLAVD EAEPERAPLA LASLADTSL                                                 | .....VQAMVSA ELCGCPW...             | -1516 |
| 2 | .....ALARA -A.....E' PEVTRG.VCG LVGCGA.....G-V-LIALE ED.....GAVQTLV.....VRELDRG GIDAPLW...                                 | -2964                               |       |
| 3 | .....AIEAN -GRAIRCEVD TSASRTEMAQ AVAQAGST.GF RG-L-LISSD ESACR.PGV PAGAVGLIA.....VQALGQA GVDAPVW...                         | -1033                               |       |
| 4 | AVNTTILEAS -ATSVR-VVA TPGADAMAL RVTDPAGHLV AT-D-LVVRG TGKWEQPEZ RGCGEGELSA.....DNGHLAEPGS TGRVVAADAS DLDLVLRSGS            | -2691                               |       |
| 5 | .....GLEQS -ATVLTCDVE ..SRSTIGT ALRAADTDL ST-V-LLSRD GEAVD.PSL DA.....LA.....VQALGQA GVERAPLN...                           | -1021                               |       |
| 6 | .....AVEKA -GRV...VVV ASADREASA.....IREVP.GEV AG-L-V.....HGRATHLA.....HOSIGEA GVERAPLN...                                  | -2459                               |       |
| 1 | .....TVI ESAVATGPFE RVNTAARGAL NGVGRVIALE HPAVWGGLV.....VPAVSGVWLA                                                         | -1569                               |       |
| 2 | .....TVI FG-DAG.SP.....VAPRDQAKL N-LGVASL.....RGPRVTLV.....LPHMPPDPLR                                                      | -3015                               |       |
| 3 | .....PEPDVAVLRY EPEGDIPRAR ARHGULTEAA LVRRNLEQEE LPGATLVLIA.....CL-OG-RTPADD DLAPPAQTYH-FAGVAGL.....LPGRNGGV.....LPESVDAAL | -1086                               |       |
| 4 | .....PEPDVAVLRY EPEGDIPRAR ARHGULTEAA LVRRNLEQEE LPGATLVLIA.....CL-OG-RTPADD DLAPPAQTYH-FAGVAGL.....LPGRNGGV.....LPESVDAAL | -2786                               |       |
| 5 | .....PEPDVAVLRY EPEGDIPRAR ARHGULTEAA LVRRNLEQEE LPGATLVLIA.....CL-OG-RTPADD DLAPPAQTYH-FAGVAGL.....LPGRNGGV.....LPESVDAAL | -2511                               |       |
| 6 | .....PEPDVAVLRY EPEGDIPRAR ARHGULTEAA LVRRNLEQEE LPGATLVLIA.....CL-OG-RTPADD DLAPPAQTYH-FAGVAGL.....LPGRNGGV.....LPESVDAAL | -1072                               |       |
| 1 | RHLAAVVSOG A.GEQLALR ADGTYGGRMV RAAAPA                                                                                     | TIDE.MR.PG FVLTWZCQG VGGCQH...      | -1642 |
| 2 | GRLT-VLAG ..SEDQV-V ADAVRAR-LG PAHVT.                                                                                      | ATSEKAVG-I-V-VZCQG VGGCQH...        | -3086 |
| 3 | RLLV-VLRGG GRAEDHL-V DGRLLGR-VV BASLPO                                                                                     | SCSRSMH-V-V-VZCQG VGGCQH...         | -1161 |
| 4 | .NLP-V...PDNPQL-L-GDDVEVP-LS PLAPSA                                                                                        | TOPAVD-V-V-VZCQG VGGCQH...          | -3171 |
| 5 | RSLA-VLAD PRGEQV-I- ADGIRVA-LV PAVARA                                                                                      | ARTR.MS-R-V-VZCQG VGGCQH...         | -1145 |
| 6 | EAVV-CLGAD G.HEDOV-I- DHARYGR-LV RAPLG.                                                                                    | TRESSME-A-A-V-VZCQG VGGCQH...       | -2584 |
| 1 | .....VETGCPDAG AGEVVAELEA HICARTHVAAC VVDRSREVRE HLGCI.GDDV HSAVEHRA                                                       | TLDDGHTL TGRHPRER ARHGRARH          | -1741 |
| 2 | .....VETGCPDAG VGD-TAELIT HGRVSH-C-VSREPREVRE LVHGLIEQGD VVNGV-VAG LPOQVHNDI DRAPEDEVA HGRGAVHED                           | EDTRELDITA                          | -3184 |
| 3 | .....VETGCPDAG GDD-LAVER HSAVHVC-C HAA...LRE HLGDE.....VIALV-HOT LTERGSISEV APEHGRHLLA HGRGAVHED                           | EDCSAEL...                          | -1248 |
| 4 | .....VETGCPDAG SDE-PARTED HSAEHTA HGRDALS A HLGDE.....VIALV-HOT LTERGSISEV APEHGRHLLA HGRGAVHED                            | EDLGRAVER                           | -3268 |
| 5 | .....VETGCPDAG ASE-BERLTA HSGVHVA-C VDGRARLEA VLAERAEGR HSGVH-VAG VETSTPDL TEAFTEDD VVNGVH-VAG                             | EDTANTGLSF                          | -3268 |
| 6 | .....VETGCPDAG AAE-EAELVA HSGVHVA-C VDGROLSK HSGVH-VAG VETSTPDL TEAFTEDD VVNGVH-VAG                                        | EDCPDLD..A                          | -1243 |
| 1 | .....VETGCPDAG AAE-EAELVA HSGVHVA-C VDGROLSK HSGVH-VAG VETSTPDL TEAFTEDD VVNGVH-VAG                                        | EDCPDART..                          | -2680 |
| 1 | .....VETGCPDAG AAE-EAELVA HSGVHVA-C VDGROLSK HSGVH-VAG VETSTPDL TEAFTEDD VVNGVH-VAG                                        | EDCPDART..                          | -2777 |
| 1 | REFLLAYTAOR PTHLEDEIDD ARAA...EQ APAEPVGA.                                                                                 | .....G RENDAREM EHGDSVWAM QUPAPCAAI | -461  |
| 2 | APAESYT-AR PRELDRIVT ..TAPSERAG EPTESILDR LASLAPAPERE BALFELVRSH                                                           | .....HGRGASA ENPADOA-A              | -1935 |
| 3 | .....HGRGASA ENPADOA-A                                                                                                     | .....HGRGASA ENPADOA-A              | -3283 |
| 4 | VLSEGFA-TR PTALFAELAG RGQARAEPD SGTPGEPAOR L-GLPRAERT AE-VRVNRV                                                            | .....HGRGASA ENPADOA-A              | -1344 |
| 5 | .....HGRGASA ENPADOA-A                                                                                                     | .....HGRGASA ENPADOA-A              | -3366 |
| 6 | REFLLAYTAOR PTHLEDEIDD ARAA...EQ SIEGPALOR L-ALSTAAER HGRGASA ENPADOA-A                                                    | .....HGRGASA ENPADOA-A              | -1341 |
| 1 | REFLLAYTAOR PTHLEDEIDD ARAA...EQ SIEGPALOR L-ALSTAAER HGRGASA ENPADOA-A                                                    | .....HGRGASA ENPADOA-A              | -2866 |
| S | GRSUNIALLY DHPTRRAID ALAAG                                                                                                 | G RENDAREM EHGDSVWAM QUPAPCAAI      | -461  |
| 1 | -VHPPTTVF D--DVRTH HLAADIGGAT GAEQAAATT                                                                                    | -486                                |       |
| 2 | -LHPSTLWF D--D-NASAVG FLDAS-GTEV RG.EAPSA                                                                                  | -1975                               |       |
| 3 | -LHPASLWF D--D-TVTAH-O HLRD-VG.. DADQAVRVRV GA                                                                             | -3418                               |       |
| 4 | -VHPPTLWF D--D-TPLAH-E HLRD-VG.. DADQAVRVRV GA                                                                             | -1484                               |       |
| 5 | -VHPPTLWF D--D-TTREI-D HYLH-VGAA EAEQAPALVR BVP                                                                            | -3505                               |       |
| 6 | -LHPATWF E--D-TVRL-D HIGG-DSGT PAREASSALR DGY                                                                              | -1480                               |       |
|   |                                                                                                                            | -2909                               |       |

Figure 31 B

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